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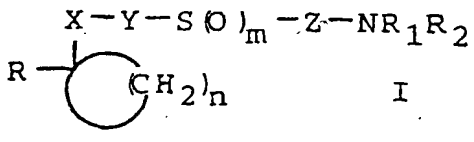

I

II

(57) Abstract: Compounds of formula (I) and pharmaceutically acceptable salts thereof in which m is 0, 1 or 2; n is 2, 3, 4 or 5; X is carbonyl or a group of formula (II) in which R_5 is H or alkyl; Y is an alkylene chain optionally substituted by one or more alkyl groups; Z is an alkylene chain containing 2 to 5 carbon atoms optionally substituted by one or more alkyl groups; R is phenyl optionally substituted by one or more halo substituents or R is naphthyl; and R_1 and R_2, which are the same or different, are H, alkyl, or arylalkyl, provided that when R_1 is benzyl, R_2 is H or methyl; have utility in the treatment of drug misuse or other addictive disorders.

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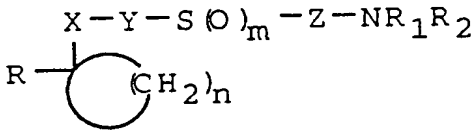
Therapeutic Agents

The present invention relates to compounds which are useful in the treatment of drug misuse or other addictive disorders.

WO94/26704 discloses compounds of formula I as given below as novel therapeutic agents, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of depression, anxiety, Parkinson's disease, obesity, cognitive disorders, seizures, neurological disorders such as epilepsy, and as neuroprotective agents to protect against conditions such as stroke. The compounds and the pharmaceutical formulations used in the present invention may be prepared as described in WO94/26704.

The present invention provides compounds of formula I



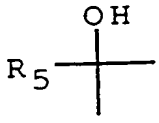
I

and pharmaceutically acceptable salts thereof in which

m is 0, 1 or 2;

n is 2, 3, 4 or 5;

X is carbonyl or a group of formula II



II

in which R_5 is H or an alkyl group containing 1 to 4 carbon atoms;

Y is an alkylene chain containing 1 or 2 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

Z is an alkylene chain containing 2 to 5 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

R is phenyl optionally substituted by one or more halo substituents which are the same or different (for example fluoro, chloro, bromo or iodo) or R is naphthyl; and

R_1 and R_2, which are the same or different, are H, a straight or branched chain alkyl group containing 1 to 4 carbon atoms, an arylalkyl group in which the alkyl group contains 1 to 3 carbon atoms, provided that when R_1 is benzyl, R_2 is H or methyl;

for use in the treatment of drug misuse or other addictive disorders.

In preferred compounds of formula I, m is 0, 1 or 2 and n is 3 or 4.

In preferred compounds of formula I, X is carbonyl or a group of formula II in which R_5 is H.

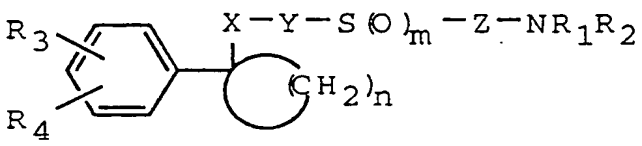
In preferred compounds of formula I, Y is methylene.

In preferred compounds of formula I, Z is an alkylene chain containing 2, 3 or 4 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms. In more preferred compounds of formula I, Z is an alkylene chain containing 2, 3 or 4 carbon atoms optionally substituted by one or more methyl groups.

In preferred compounds of formula I, R is phenyl substituted by one or two chloro substituents, or R is naphthyl. In more preferred compounds of formula I, R is 3-chlorophenyl, 3,4-dichlorophenyl or 2-naphthyl.

In preferred compounds of formula I, R_1 is an alkyl group containing 1 to 3 carbon atoms or is benzyl, and R_2 is an alkyl group containing 1 to 3 carbon atoms. In more preferred compounds of formula I, R_1 and R_2 are both methyl or ethyl or R_1 is benzyl and R_2 is methyl. In especially preferred compounds of formula I, R_1 and R_2 are both methyl.

A preferred group of compounds of formula I is represented by formula III



III

and pharmaceutically acceptable salts thereof in which m, n, X, Y, Z, R_1 and R_2 are as described above for formula I;

and R_3 is halo (for example fluoro, chloro, bromo or iodo), and R_4 is H or halo (for example fluoro, chloro, bromo or iodo), or R_3 and R_4 together with the carbon atoms to which they are attached form a fused benzene ring.

In more preferred compounds of formula III, R_3 is chloro and R_4 is H, R_3 and R_4 are both chloro or R_3 and R_4 together with the carbon atoms to which they are attached form a fused benzene ring. In especially preferred compounds of formula III, R_3 is chloro situated in the 3-substitution position on the phenyl ring and R_4 is H, R_3 and R_4 are both chloro and are situated in the 3- and 4- substitution positions on the phenyl ring respectively, or R_3 and R_4 together with the phenyl ring to which they are attached form a 2-naphthyl group.

Compounds of formula I and III may exist as salts with pharmaceutically acceptable acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. Compounds of formula I and III and their salts may exist in the form of solvates (for example hydrates).

Certain compounds of formula I and III may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

It will be appreciated by those skilled in the art that compounds of formula I and III may contain one or more chiral centres. When compounds of formulal and III contain one chiral centre, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of those enantiomers. The individual enantiomers may be obtained by methods known to those skilled in

the art. Such methods typically include resolution via formation of diastereoisomeric salts which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; via selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification, oxidation or reduction; or via gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When compounds of formula I and III contain more than one chiral centre, the compounds may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and III and mixtures thereof.

Specific compounds of formula I and III are:-

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylsulphinyl]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylsulphonyl]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(diethylamino)ethylthio]ethanone;

2-[2-(N-benzyl-N-methylamino)ethylthio]-1-[1-(3,4-dichlorophenyl)cyclobutyl]-ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylthio]ethanol;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylsulphonyl]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanol;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)-2-methylpropylthio]-ethanone;

2-[2-(dimethylamino)ethylthio]-1-[1-(2-naphthyl)cyclobutyl]ethanone;

1-[1-(3-chlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[4-(dimethylamino)butylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dipropylamino)propylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)-2-methylpropylthio]ethanol;

1-[1-(3,4-dichlorophenyl)cyclopentyl]-2-[3-(dimethylamino)propylthio]ethanone;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

Specific enantiomeric forms of compounds of formula I and III are:

(-)-1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanol;

(+)-1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanol;

The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or III together with a pharmaceutically acceptable diluent or carrier.

As used hereinafter, the term "active compound" denotes a compound of formula I or III. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form.

Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups, solutions and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example micro-crystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethyl cellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound.

Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethyl- cellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable

oil, for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, for example an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt of a compound of formula I or III or (b)solid in the form of an implanted support, for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containingall the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be

such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I or III may be used to treat drug misuse or other addictive disorders. Whilst the precise amount of active compound administered in such treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history, and always lies within the sound discretion of the administering physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in single or divided doses at one or more times during the day.

In another aspect the present invention provides a method of treating drug misuse or other addictive disorders which comprises the administration of a therapeutically effective amount of a compound of formula I to a patient in need thereof.

The present invention provides a method of reducing cravings to food or an addictive substance in a mammal comprising administering an effective amount of a compound of formula I to a mammal in need thereof.

Suitably the addictive substance is cocaine, amphetamine, nicotine, opiates, tobacco or alcohol. The addictive substance may also be MDMA (ecstasy), a cannabinoid, LSD, MDA or PCP. The term opiates includes heroin and morphine.

In yet another aspect, the present invention provides the use of a compound of formula I or III in the manufacture of a medicament for use in the treatmentof drug misuse or other addictive disorders.

Conditions which may be advantageously treated with the compounds of the present invention include disorders arising from drug misuse including drug withdrawal symptoms, aiding in the cessation of smoking, aiding in the prevention of relapse after cessation of drug use and similar use in the treatment of other addictive disorders such as compulsive gambling, compulsive shopping disorder and compulsive sexual disorder.

In another aspect the present invention provides a method of treating addictive-drug-induced psychoses comprising administering a therapeutically effective amount of a compound of formula I to a mammal, particularly a human being, in need thereof. The addictive drug is selected from one or more of the following: a benzodiazepine; a cannabinoid, LSD, MDMA, MDA, PCP, an opiate including heroin and morphine, amphetamine, cocaine and alcohol.

The pharmacological activity of the compounds of the present invention may be demonstrated by one or more of the following tests.

STUDY 1 METHODS

Subjects: The subjects are four male rhesus monkeys *(Macaca mulatta)*, weighing 5.7-8.1 kg and maintained on a diet of 3-4 monkey biscuits and one piece of fresh fruit per day. During the week, all food is delivered after the experimental session, whereas at weekends, food is delivered between 9 a.m. and noon. Water is freely available at all times. The monkeys are housed in a humidity and temperature controlled room with a 12 h light-dark cycle (lights on from 7 a.m. to 7 p.m.).

Apparatus: Each monkey is housed individually in a well-ventilated, stainless steel chamber (56 x 71 x 69 cm) which includes an operant panel (28 x 28 cm) mounted on the front wall. Three response keys are arranged in a horizontal row 3.2 cm from the top of the operant panel. Each key can be transilluminated by red or green stimulus lights (Superbright LEDs). An externally mounted pellet dispenser delivers 1 g fruit-flavoured food pellets to a food receptacle beneath the operant response panel. A computer, located in a separate room, controls the operant panels and data collection.

Discrimination Training: Discrimination training is conducted 5 days per week during daily sessions composed of multiple cycles. Each cycle consists of a 15 min time-out period followed by a 5 min response period. During the time-out, all stimulus lights are off, and responding has no scheduled consequences. During the response period, the right and left response keys are transilluminated red or green, and monkeys can earn up to 10 food pellets by responding under a FR 30 schedule of food presentation. For one monkey, the left key is illuminated green and the right key is illuminated red, the colours of the response-keys are reversed for the other three monkeys. The centre key is not illuminated at any time and responding on it has no scheduled consequences. If all available food pellets are delivered before the end of the 5 min response period, the stimulus lights are turned off and responding has no scheduled consequences for the remainder of the 5 min period.

On training days, monkeys are given either saline or 0.40 mg/kg cocaine, i.m., 10 min before the response period. Following the administration of saline, responding on only the green key (the saline-appropriate key) produces food, whereas following administration of 0.40 mg/kg cocaine, only responding on the red key (the drug-appropriate key) produces food. Responses on the inappropriate key reset the FR requirement on the appropriate key. Sessions consist of 1 to5 cycles and, if cocaine is administered, this occurs only during the last cycle. Thus, training days consist of 0 to 5 saline cycles followed by 0 or 1 cocaine cycle.

During each response period, 3 dependent variables are determined:

1) Percent injection-appropriate responding prior to delivery of the first reinforcer.

2) Percent injection-appropriate responding for the entire response period

3) Response Rate.

Monkeys meeting the following criteria during the training day immediately proceeding the test day and in at least 6 of 7 consecutive training sessions before this are used for discrimination testing:

1) the percent injection-appropriate responding prior to delivery of the first

reinforcer is ≥ 80% for all cycles;

2) the percent injection-appropriate responding for the entire cycle is ≥ 90% for all cycles;

3) Response rates during saline training cycles are >0.5 responses per second.

If responding did not meet criterion levels of discrimination performance, then training is continued until criterion levels of performance are obtained for at least two consecutive days.

Discrimination Testing: Test sessions are identical to training sessions except that responding on either key produces food, and the test compound is administered using a Pretreatment Protocol. In this protocol, a cumulative dose-effect curve for cocaine (0.013-1.3 mg/kg) is determined either alone or following pretreatment with the test compound, which is administered 20 min before the first dose of cocaine.

Mean data from saline and drug cycles during the training day immediately proceeding the initial test day serve as the control data for the subsequent test day.

Data Analysis: The Percent Cocaine-Appropriate Responding and the Response Rate are plotted as a function of the dose of cocaine (log scale). Where possible, the ED_{50} value for cocaine is determined by drawing a line between the points above and below 50% cocaine-appropriate responding, and then using linear regression to interpolate the dose that would produce 50% cocaine-appropriate responding. ED_{50} values for cocaine administered alone and following pretreatment with the test compound are then compared.

Drugs: Cocaine hydrochloride is dissolved in sterile saline. The test compound is dissolved in 1% lactic acid in distilled water.

RESULTS

Control mean saline-appropriate responding = 99.8% (± 0.2) and 100% appropriate responding are obtained during cocaine cycles.

ED_{50} values for cocaine are calculated. Administration of cocaine alone produces a dose-dependent increase in cocaine-appropriate responding in all four monkeys. Complete substitution is obtained at the training dose of cocaine (0.4 mg/kg) in all monkeys, and a higher dose of 1.3 mg/kg usually decreases response rates. Pretreatment with 0.01 mg/kg of the test compound produces a rightward shift in the cocaine dose-effect curve and a 3-fold increase in the cocaine ED_{50} value in monkey 2, but it has no effect on the cocaine discrimination dose-effect curve in the other three monkeys. A higher dose of 0.032 mg/kg of the test compound produces rightward shifts in the cocaine dose-effect curves in all four monkeys. The test compound (0.01 and 0.032 mg/kg) also eliminated responding during the first one to three cycles of the cumulative cocaine dose-effect curve determination (i.e. in combination with 0.013 and 0.04 mg/kg cocaine). However, monkeys responded after administration of higher cocaine doses, thereby permitting evaluation of the effects on cocaine discrimination. Interestingly, response rates following administration of the highest dose of cocaine (1.3 mg/kg) are often higher following test compound pretreatment than for cocaine alone, suggesting that the test compound attenuated the rate-decreasing effects of high cocaine doses.

These studies can establish that the test compound antagonises the discriminative stimulus effects and possibly also the rate decreasing effects of cocaine at doses that also produce effects on response rates by comparing ED_{50} values (mg/kg) for cocaine administered either alone or after pretreatment with test compound.

STUDY 2 METHODS

Subjects: The subjects are four male rhesus monkeys *(Macaca mulatta)*. Each monkey is maintained on a diet of 3 monkey biscuits and one piece of fresh fruit per day in addition to fruit-flavoured pellets delivered during operant sessions (see below). Water is freely available at all times. The monkeys are housed in a humidity

and temperature controlled room with a 12 hr light-dark cycle (lights on from 7 a.m. to 7 p.m.).

Monkeys are surgically implanted with double-lumen silicone rubber catheters (inside diameter 0.7 mm, outside diameter 2.0 mm) to facilitate concurrent delivery of cocaine and treatment compounds. Catheters are implanted in the jugular or femoral vein and exteriorized in the midscapular region. All surgical procedures are performed under aseptic conditions. Monkeys are sedated with ketamine (5 mg/kg, s.c.), and anaesthesia is induced with sodium thiopental (10 mg/kg, i.v). Monkeys receive 0.05 mg/kg atropine, to reduce salivation. Following insertion of a tracheal tube, anaesthesia is maintained with isoflurane (1-1.5% in oxygen). After surgery, monkeys are administered aspirin or acetaminophen (80-160 mg/day; p.o.) for 3 days and Procaine Penicillin 0 (300,000 units/day, i.m.) every day for 5 days. The i.v. catheter is protected by a tether system consisting of a custom-fitted nylon vest connected to a flexible stainless steel cable and fluid swivel (Lomir Biomedical; Malone, NY), which permits the monkeys to move freely. Catheter patency is periodically evaluated by i.v. administration of the short-acting barbiturate methohexital (3 mg/kg i.v.) or ketamine (2-3 mg/kg i.v.). The catheter is considered patent if i.v. administration of methohexital or ketamine produces loss of muscle tone within 10 seconds after its administration.

Apparatus: Each monkey is housed individually in a well-ventilated stainless steel chamber (64 x 64 x 79 cm which includes an operant panel (28 x 28 cm) mounted on the front wall. Three response keys (6.4 x 6.4 cm) are arranged in a horizontal row 3.2 cm from the top of the operant panel. Each key can be transilluminated by red or green stimulus lights (Superbright LEDs). An externally mounted pellet dispenser delivers 1 g fruit-flavoured food pellets to a food receptacle beneath the operant response panel. Two syringe pumps are mounted above each cage for delivery of saline or drug solutions through the intravenous catheters. Operant panels and data collection are controlled by a computer through a MED-PC interface.

Training: As shown in the diagram below, food and i.v. drug or saline injections are available during three alternating components: a 5 min food component, a 100-min drug component, and a second 5 min food component. Both food and i.v. injections are available under a FR 30 schedule of reinforcement.

During the two food components, the response key is transilluminated red. During the drug component, the response key is transilluminated green. Following the delivery of each food pellet or drug injection, there is a 10 sec timeout period, during which the stimulus light illuminating the centre response key is turned off and responding has no scheduled consequences. The food and drug components are separated by 5-min timeout periods when the response key is dark, and responding has no scheduled consequences. The entire food/drug/food session lasts 120 min.

In addition to the food/drug/food session described above, monkeys are also given the opportunity to self-administer additional food pellets during supplementary food sessions. During these sessions, food is available under a FR30/Timeout 10 sec schedule, and a maximum of 25 pellets per session can be earned. These food sessions provide additional enrichment opportunities for the monkeys and behavioural information relevant for the evaluation of prolonged treatment drug effects.

During training, the solution available for self-administration during the drug component is alternated between 0.032 mg/kg/inj cocaine (the maintenance dose of cocaine) and saline. Each period of cocaine or saline availability usually lasts from 3 to 10 days. Monkeys are trained until they met the following criteria for stable cocaine self-administration: 1) three consecutive days during which the response rate during the drug component of each session differs by no more than 20% from the mean drug component response rate and there is no upward or downward trend; and 2) rapid saline extinction as indicated by a decrease in drug component response rates on the first day of saline substitution.

Evaluation of Test Compound: The effects of the test compound (0.0032-0.10 mg/kg) on cocaine self-administration and food-maintained behaviour are evaluated using the standard pretreatment test procedure. In this procedure, the test compound is administered i.m. 20-min prior to a test session during which a test unit dose of cocaine is available during the drug component. Two series of studies are described here. In the first, the unit dose of cocaine is 0.0032 mg/kg/inj (at or near the peak of each monkey's cocaine self-administration dose-effect curve) and the effects of pretreatment with each dose of test compound are determined in single sessions for all monkeys. In the second series of studies, the effects of pretreatment with each of two doses of the test compound (0.003 and 0.01 mg/kg) on the entire

cocaine dose-effect function are determined. In these studies, the dose of cocaine is systematically varied for single test sessions after pretreatment with each dose of the test compound. Both the dose of cocaine and the pretreatment dose of the test compound are varied across test sessions in an irregular order among monkeys.

At the conclusion of each pretreatment test in either series of studies, training conditions (availability of saline or the maintenance dose of cocaine) are reinstated. Test sessions generally are conducted on Tuesdays and Fridays, and either saline or the maintenance dose of cocaine is available during training sessions for the remainder of the week. On occasion, another dose of cocaine is substituted for the maintenance dose to insure that the position of the cocaine dose-effect function in individual monkeys is stable. In addition, test days are occasionally omitted to allow several days of saline substitution.

Data Analysis: The dependent variables are the response rates during each food and drug component. The response rate is calculated as [total # responses (component duration - S timeouts)]. Control response rates for each food and drug component during availability of each unit dose of cocaine are defined as the response rate obtained when that unit dose of cocaine is available and no pretreatment is administered. The ED_{50} value for the test compound during each food or drug component is defined as the dose of the test compound that decreases rates of cocaine or food self-administration to 50% of control response rates. The ED_{50} values are determined where possible by linear regression from the linear portion of the test compound dose-effect curve.

For subsequent studies, in which the unit dose of cocaine is varied and the pretreatment dose of the test compound is held constant, response rates are graphed as a function of the unit dose of cocaine. Control cocaine dose-effect curves are determined in the absence of pretreatment and are visually compared to cocaine dose-effect curves determined following pretreatment with the test compound.

Drugs: Cocaine hydrochloride is dissolved in saline. A stock solution of 10 mg/ml of the test compound is prepared using a vehicle of 1% lactic acid in distilled water, and dilutions are made with distilled water. Aseptic precautions are taken in every phase of cocaine solution preparation and dispensing. Cocaine solutions are

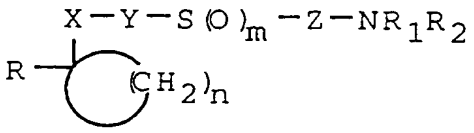
filter-sterilised using a 0.22 micron Millipore Filter and stored in sterile, pyrogen-free vials. Sterility of the entire fluid path for drug solutions is maintained throughout the study. Each unit dose of cocaine is delivered i.v. in an injection volume of 0.1 ml. Doses of the test compound are delivered i.m. in a volume of 0.2-3.0 ml.

5

These studies can establish that treatment with the test compound diminishes cocaine self-administration and food-maintained behaviour.

Claims

1) Compounds of formula I



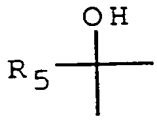
I

and pharmaceutically acceptable salts thereof in which

m is 0, 1 or 2;

n is 2, 3, 4 or 5;

X is carbonyl or a group of formula II



II

in which R_5 is H or an alkyl group containing 1 to 4 carbon atoms;

Y is an alkylene chain containing 1 or 2 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

Z is an alkylene chain containing 2 to 5 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

R is phenyl optionally substituted by one or more halo substituents (for example fluoro, chloro, bromo or iodo) or R is naphthyl; and

R_1 and R_2, which are the same or different, are H, a straight or branched chain alkyl group containing 1 to 4 carbon atoms, an arylalkyl group in which the

alkyl group contains 1 to 3 carbon atoms, provided that when R_1 is benzyl, R_2 is H or methyl;
for use in the treatment of drug misuse or other addictive disorders.

2) The use of compounds of formula I as claimed in claim 1 in which m is 0,1 or 2 and n is 3 or 4.

3) The use of compounds of formula I as claimed in any preceding claim in which X is carbonyl or a group of formula II in which R_5 is H.

4) The use of compounds of formula I as claimed in any preceding claim in which Y is methylene.

5) The use of compounds of formula I as claimed in any preceding claim in which Z is an alkylene chain containing 2,3 or 4 carbon atoms optionally substitited by one or more alkyl groups containing 1 to 3 carbon atoms .

6) The use of compounds of formula I as claimed in any preceding claim in which Z is an alkylene chain containing 2,3 or 4 carbon atoms optionally substitited by one or more methyl groups.

7) The use of compounds of formula I as claimed in any preceding claim in which R is phenyl substituted by one or two chloro substituents or R is naphthyl.

8) The use of compounds of formula I as claimed in any preceding claim in which R is 3-chlorophenyl, 3,4-dichlorophenyl or 2-naphthyl.

9) The use of compounds of formula I as claimed in any preceding claim in which R_1 is an alkyl group containing 1 to 3 carbon atoms or is benzyl, and R_2 is an alkyl group containing 1 to 3 carbon atoms.

10) The use of compounds of formula I as claimed in any preceding claim in which R_1 and R_2 are both methyl or ethyl or R_1 is benzyl and R_2 is methyl.

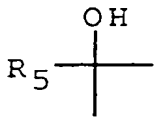
11) The use of compounds of formula III

and pharmaceutically acceptable salts thereof in which

m is 0, 1 or 2;

n is 2, 3, 4 or 5;

X is carbonyl or a group of formula II



II

in which R_5 is H or an alkyl group containing 1 to 4 carbon atoms;

Y is an alkylene chain containing 1 or 2 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

Z is an alkylene chain containing 2 to 5 carbon atoms optionally substituted by one or more alkyl groups containing 1 to 3 carbon atoms;

R_1 and R_2, which are the same or different, are H, a straight or branched chain alkyl group containing 1 to 4 carbon atoms, an arylalkyl group in which the alkyl group contains 1 to 3 carbon atoms, provided that when R_1 is benzyl, R_2 is H or methyl;

and R_3 is halo, and R_4 is H or halo, or R_3 and R_4 together with the carbon atoms to which they are attached form a fused benzene ring.

12) The use of compounds of formula III as claimed in claim 11 in which R_3 is chloro and R_4 is H, R_3 and R_4 are both chloro or R_3 and R_4 together with the carbon atoms to which they are attached form a fused benzene ring.

13) The use of compounds of formula III as claimed in any preceding claim in which R_3 is chloro situated in the 3-substitution position on the phenyl ring and R_4 is

H, R_3 and R_4 are both chloro and are situated in the 3- and 4-substitution positions on the phenyl ring respectively, or R_3 and R_4 together with the phenyl ring to which they are attached form a 2-naphthyl group.

14) The use of compounds of formula I as claimed in claim 1 which are:

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylsulphinyl]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylsulphonyl]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(diethylamino)ethylthio]ethanone;

2-[2-(N-benzyl-N-methylamino)ethylthio]-1-[1-(3,4-dichlorophenyl)cyclobutyl]-ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[2-(dimethylamino)ethylthio]ethanol;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylsulphonyl]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanol;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)-2-methylpropylthio]-ethanone;

2-[2-(dimethylamino)ethylthio]-1-[1-(2-naphthyl)cyclobutyl]ethanone;

1-[1-(3-chlorophenyl)cyclobutyl]-2-[3-(dimethylamino)propylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[4-(dimethyl- amino)butylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dipropyl- amino)propylthio]ethanone;

1-[1-(3,4-dichlorophenyl)cyclobutyl]-2-[3-(dimethylamino)-2-methylpropylthio]ethanol;

1-[1-(3,4-dichlorophenyl)cyclopentyl]-2-[3-(dimethylamino)propylthio]ethanone;

and pharmaceutically acceptable salts thereof in the form of individual enantiomers, racemates, or other mixtures of enantiomers.

15) Pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I as claimed in claim 1, together with a pharmaceutically acceptable diluent or carrier.

16) A method of treating drug misuse or other addictive disorders which comprises the administration of a therapeutically effective amount of a compound of formula I as defined in any one of claims 1 to 14 to a patient in need thereof.

17) A method of reducing cravings to food or an addictive substance in a mammal comprising administering an effective amount of a compound of formula I as defined in any one of claims 1 to 14 to a mammal in need thereof.

18) A method as claimed in claim 17 wherein the addictive substance is cocaine, amphetamine, nicotine, opiates, tobacco, alcohol or ecstasy.

19) The use of a compound of formula I as claimed in any of claims 1 to 14 in the manufacture of a medicament for use in the treatment of drug misuse or other addictive disorders

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
2475/002630		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 05736	21/06/2000	05/07/1999
Applicant		
KNOLL AKTIENGESELLSCHAFT		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

Intern: ial Application No
PCT/EP 00/05736

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/145 A61P25/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 26327 A (SMITHKLINE BEECHAM) 5 October 1995 (1995-10-05) the whole document	1-19
A	WO 98 29411 A (KNOLL) 9 July 1998 (1998-07-09) the whole document	1-19
A	WO 94 26704 A (BOOTS) 24 November 1994 (1994-11-24) cited in the application claims 15,20	1-19

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 2000	06/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
PCT/EP 00/05736

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9526327 A	05-10-1995	AU 2071095 A	17-10-1995
		DE 69510192 D	15-07-1999
		DE 69510192 T	24-02-2000
		EP 0752981 A	15-01-1997
		JP 9510719 T	28-10-1997
		US 5817698 A	06-10-1998
WO 9829411 A	09-07-1998	AU 5758098 A	31-07-1998
		BG 103557 A	30-06-2000
		BR 9714237 A	18-04-2000
		CN 1247537 A	15-03-2000
		EP 0948498 A	13-10-1999
		NO 993172 A	25-06-1999
		PL 334254 A	14-02-2000
		ZA 9711551 A	23-06-1999
WO 9426704 A	24-11-1994	AT 172719 T	15-11-1998
		AU 681669 B	04-09-1997
		AU 6843394 A	12-12-1994
		BG 61913 B	30-09-1998
		BG 100127 A	31-07-1996
		BR 9406577 A	30-01-1996
		CA 2162706 A	24-11-1994
		CZ 9502936 A	12-06-1996
		DE 69414264 D	03-12-1998
		DE 69414264 T	25-03-1999
		DK 715620 T	05-07-1999
		EP 0715620 A	12-06-1996
		ES 2124411 T	01-02-1999
		FI 955429 A	03-01-1996
		HU 211124 B	30-10-1995
		IL 109635 A	10-03-1998
		JP 8510222 T	29-10-1996
		LV 11320 A	20-06-1996
		NO 954542 A	10-01-1996
		NZ 266776 A	26-02-1998
		PL 311628 A	04-03-1996
		RO 115519 A	30-03-2000
		RU 2135467 C	27-08-1999
		SK 140795 A	04-09-1996
		US 5652271 A	29-07-1997
		ZA 9403241 A	14-11-1994

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2475/002630		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05736	21/06/2000	05/07/1999
International Patent Classification (IPC) or national classification and IPC A61K31/145		
Applicant KNOLL AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/12/2000	19.06.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fayos, C Telephone No. +49 89 2399 2180

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05736

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-16 as originally filed

Claims, No.:

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2-13 (completely) and 16-18 (industrial applicability).

because:

☒ the said international application, or the said claims Nos. 16-18 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 2-13 (completely) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1 and 15-19
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1 and 15-19
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1 and 15 ; 16-19 see separate sheet

No: Claims -

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1- Claims 2-10 have been drafted as claims dependent on claim 1. However, claim 1 refers to "Compounds of formula I ... for use in the treatment of drug misuse or other addictive disorders", whereas claims 2-10 refer to "the use of compounds of formula I". Claims 2-10 lack therefore clarity (Art. 6 PCT) in that the dependency of said claims is not clear. Hence, no opinion will be formulated with regards to the novelty, inventive step and industrial applicability of claims 2-10. The same applies to claim 14.

2- Claim 11 and dependent claims 12-13 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims refer to "the use of compounds of formula III" without mentioning what said use is (the claim appears to be lacking a verb). Hence, said claims further lack support (Art. 5 PCT). Hence, no opinion will be formulated with regards to the novelty, inventive step and industrial applicability of claims 11-13.

3- Claims 16-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

NOVELTY - Art. 33 (1) and (2) PCT

4- Claims 1, and 15-19 appear to be novel over the prior art cited in the search report.

4.1- The novel feature is: pharmaceutical compositions comprising a compound of formula I for the treatment of drug misuse or other addictive disorders.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

5- Claims 1, and 15-19 appear to be inventive in the light of the prior art cited in the search report.

5.1- The prior art cited in the search report does not suggest pharmaceutical compositions comprising a compound of formula I for the treatment of drug misuse or other addictive disorders.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

6- Claims 1 and 15 appear to be industrially applicable.

6.1- For the assessment of the present claims 16-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NASH, David, Allan
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
ROYAUME-UNI

Date of mailing (day/month/year)
19 September 2001 (19.09.01)

Applicant's or agent's file reference
2475/002630

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/05736

International filing date (day/month/year)
21 June 2000 (21.06.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address
GOLDSCHEID, Bettina
BASF Aktiengesellschaft
D-67056 Ludwigshafen
Germany

State of Nationality:
State of Residence:
Telephone No.: 0621/60-78916
Facsimile No.: 0621/60-21183
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
NASH, David, Allan
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
United Kingdom

State of Nationality:
State of Residence:
Telephone No.: +44-117 910 3200
Facsimile No.: +44-117 910 3201
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Gabriele BAEHR
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NASH, David, Allan
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
ROYAUME-UNI

Date of mailing (day/month/year)
31 octobre 2001 (31.10.01)

Applicant's or agent's file reference
2475/002630

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/05736

International filing date (day/month/year)
21 juin 2000 (21.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
KNOLL AKTIENGESELLSCHAFT
D-67061 Ludwigshafen
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address
KNOLL GMBH
D-67061 Ludwigshafen
Germany

State of Nationality: DE
State of Residence: DE
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
François BAECHLER
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 February 2001 (14.02.01)	
International application No. PCT/EP00/05736	**Applicant's or agent's file reference** 2475/002630
International filing date (day/month/year) 21 June 2000 (21.06.00)	**Priority date** (day/month/year) 05 July 1999 (05.07.99)
Applicant LUSCOMBE, Graham, Paul et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 December 2000 (15.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer R. E. Stoffel
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

NASH, David, Allan
Haseltine Lake & Co.
Imperial House
15-19 Kingsway
London WC2B 6UD
ROYAUME-UNI

Date of mailing (day/month/year) 31 October 2001 (31.10.01)	
Applicant's or agent's file reference 2475/002630	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/05736	**International filing date** (day/month/year) 21 June 2000 (21.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
KNOLL AKTIENGESELLSCHAFT D-67061 Ludwigshafen Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
KNOLL GMBH D-67061 Ludwigshafen Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer François BAECHLER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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